

U.S.S.N. 09/445,439

Filed: February 23, 2000

AMENDMENT AND RESPONSE TO OFFICE ACTION

In the Claims

Claim 1-100 (canceled)

101. (Currently amended) A method ~~for preparing a drug targeting system for~~
~~administering one or more physiologically effective substances to a mammal, said~~
method comprising of administering one or more physiologically effective substances to
the central nervous system comprising

a) administering to a patient in need thereof nanoparticles consisting essentially
of a polymeric material comprising one or more monomeric or oligomeric precursors
polymerized in the presence of one or more stabilizers, and loaded with one or more
physiologically effective substances, said one or more wherein the stabilizers being are
selected from the group consisting of polysorbate 85, polysorbate 81, dextran 12,000,
carboxylic acid esters of glycerol, sorbitan monostearate, sorbitan monooleate,
polyoxamer 188, polyoxamines, alkoxyated ethers, alkoxyated esters, alkoxyated
mono-, di-, and triglycerides, alkoxyated phenols and diphenols, Genapol® compounds,
Bauki® compounds sodium stearate, metal salts of carboxylic acids, metal salts of
alcohol sulfates, metal salts of sulfosuccinates, ~~wherein said Genapol® and~~ compounds
are of the formula

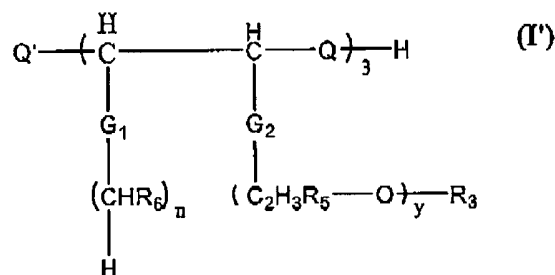
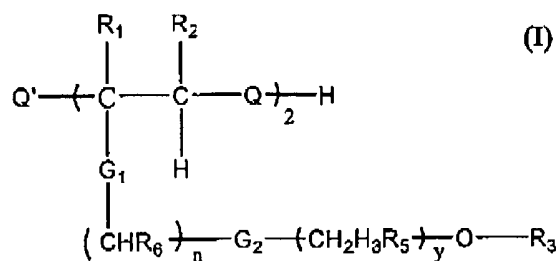


wherein y is in the range of 4 to 18 and x is in the range of 1 to 18,
compounds of the formula (I) or (I')

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in which wherein R_1 , R_2 , R_5 , and R_6 are identical or different and represent hydrogen and a methyl or ethyl group,

wherein Q represents a valency, oxygen or an ester or amide bridge and Q' denotes hydrogen if Q represents a valency or oxygen, and is a hydroxyl or amino group if Q represents an ester or amide bridge,

wherein X is an integer from 3 to 50, if Q is a valency or oxygen, and an integer from 3 to 1000 if Q is an ester or amide function, and

wherein G_1 and G_2 are a valency oxygen or an ester or amide group, it being possible for the two groups to be identical or different, n is an integer from 4 to 44, y is an integer from 2 to 50, and R_3 is hydrogen or a lower alkyl having 1-6 C atoms, and mixtures of two or more said substances, and; by polymerizing one or more monomers or oligomeric precursors of said polymer material or both, in the presence of said one or more physiologically effective substances and in the presence of said stabilizers; and optionally

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~~b) providing said nanoparticles in a medium allowing the transport of said nanoparticles to a target within or on said mammal after administration.~~

102. (currently amended) A method for preparing a ~~drug targeting system for a~~ nanoparticle formulation for administering one or more physiologically effective substances to a ~~mammal~~, said method comprising: the central nervous system comprising:

a) ~~nanoparticles made of a polymeric material, said nanoparticles being free of a surfactant surface coating and comprising said polymeric material, one or more physiologically effective substances to be delivered to said mammal, and one or more stabilizers for said nanoparticles allowing targeting of said one or more physiologically effective substances to a specific site within or on a mammalian body, providing nanoparticles consisting essentially of a polymeric material comprising one or more monomeric or oligomeric precursors polymerized in the presence of one or more stabilizers, and loaded with one or more physiologically effective substances said one or more wherein the stabilizers being are selected from the group consisting of polysorbate 85, polysorbate 81, dextran 12,000, carboxylic acid esters of glycerol, sorbitan monostearate, sorbitan monooleate, polyoxamer 188, polyoxamines, alkoxyated ethers, alkoxyated esters, alkoxyated mono-, di-, and triglycerides, alkoxyated phenols and diphenols, Genapol® compounds, Bauli® compounds, sodium stearate, metal salts of carboxylic acids, metal salts of alcohol sulfates, metal salts of sulfosuccinates, wherein said Genapol® and compounds are of the formula~~



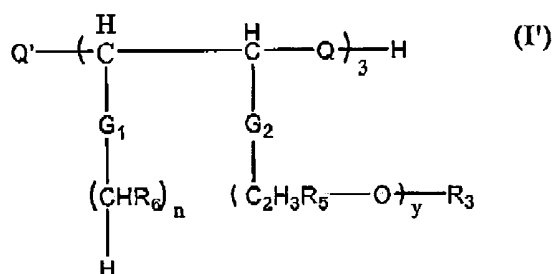
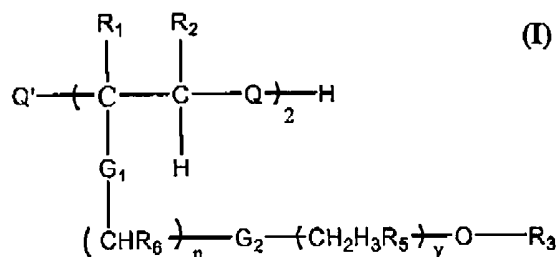
wherein y is in the range of 4 to 18 and x is in the range of 1 to 18,

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compounds of the formula (I) or (I')



~~in which~~ wherein R₁, R₂, R₅, and R₆ are identical or different and represent hydrogen and a methyl or ethyl group,

wherein Q represents a valency, oxygen or an ester or amide bridge and Q' denotes hydrogen if Q represents a valency or oxygen, and is a hydroxyl or amino group if Q represents an ester or amide bridge,

wherein X is an integer from 3 to 50, if Q is a valency or oxygen, and an integer from 3 to 1000 if Q is an ester or amide function,

wherein G₁ and G₂ are a valency oxygen or an ester or amide group, it being possible for the two groups to be identical or different, n is an integer from 4 to 44, y is an integer from 2 to 50, and R₃ is hydrogen or a lower alkyl having 1-6 C atoms, and mixtures of two or more said substances, and; by polymerizing one or more monomers or oligomeric precursors of said polymer material or both, in the presence of said one or

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more physiologically effective substances and in the presence of said stabilizers; and optionally

b) loading an effective amount of one or more physiologically effective substances to be delivered to ~~said mammal~~ the central nervous system of the patient into or onto ~~said~~ the nanoparticles or both; and optionally

c) providing ~~said~~ the nanoparticles in a medium allowing the transport of ~~said~~ the nanoparticles to a target ~~within or on said mammal~~ the central nervous system of a patient after administration.

103. (currently amended) The method of claim 101, wherein ~~said~~ the polymerization step is selected from the group consisting of emulsion polymerization, interfacial polymerization, solvent deposition, solvent evaporation and crosslinking oligomers or polymers or both, in solution.

104. (previously presented) The method according to claim 101, wherein, in the polymerization step, a polymeric material is formed which is selected from the group consisting of polyacrylates, polymethacrylates, polycyanoacrylates, polyarylamides, polyacetates, polyglycolates, polyanhydrides, polyorthoesters, gelatin, polysaccharides, albumin, polystyrenes, polyvinyls, polyacrolein, polyglutaraldehydes and copolymers and mixtures thereof.

105. (currently amended) The method of claim ~~101~~ 102, wherein ~~said~~ the loading step comprises mixing ~~said~~ the nanoparticles with a solution of one or more physiologically effective substances and allowing a sufficient time for an effective amount of ~~said one or more~~ the physiologically effective substances to be adsorbed onto or absorbed by ~~said~~ the nanoparticles or both.

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106. (currently amended) The method of claim 101 wherein ~~said~~ the polymerization step is selected from the group consisting of emulsion polymerization, interfacial polymerization, solvent deposition, solvent evaporation and crosslinking oligomers or polymers or both, in solution.

107. (previously presented) The method according to claim 101, wherein, in the polymerization step, a polymeric material is formed which is selected from the group consisting of polyacrylates, polymethacrylates, polycyanoacrylates, polyarylamides, polyacetates, polyglycolates, polyanhydrides, polyorthoesters, gelatin, polysaccharides, albumin, polystyrenes, polyvinyls, polyacrolein, polyglutaraldehydes and copolymers and mixtures thereof.

108. (currently amended) The method of claim 102, wherein said the loading step comprises mixing said the nanoparticles with a solution of said one or more physiologically effective substances and allowing a sufficient time for an effective amount of said ~~one or more~~ the physiologically effective substances to be adsorbed onto or absorbed by said the nanoparticles or both.

109. (currently amended) The method of claim 101, wherein said ~~one or more~~ the stabilizers are selected from the group consisting of polysorbate 85 and dextran 12,000 and mixtures thereof ~~and mixtures of said stabilizers with other stabilizers.~~

110. (currently amended) The method of claim 102, wherein said ~~one or more~~ the stabilizers are selected from the group consisting of polysorbate 85 and dextran 12,000 and mixtures thereof ~~and mixtures of said stabilizers with other stabilizers.~~

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111. (currently amended) The method of claim 101, wherein ~~said one or more~~ the physiologically effective substances are selected from the group consisting of a therapeutic substance and a diagnostic substance.

112. (currently amended) The method of claim 102, wherein ~~said one or more~~ the physiologically effective substances are selected from the group consisting of a therapeutic substance and a diagnostic substance.

113. (currently amended) The method of claim 101, wherein ~~said one or more~~ the physiologically effective substances have central nervous system activity but cannot cross the blood brain barrier without modification or without a carrier.

114. (currently amended) The method of claim 102, wherein ~~said one or more~~ the physiologically effective substances have central nervous system activity but cannot cross the blood brain barrier without modification or without a carrier.

115. (currently amended) The method of claim 101, wherein ~~said one or more~~ the physiologically effective substances are selected from the group consisting of drugs acting at synaptic sites and neuroeffector junctional sites, general and local analgesics; hypnotics and sedatives, drugs for the treatment of psychiatric disorder; anti-epileptics and anti-convulsants; drugs for the treatment of Parkinson's and Huntington's disease, aging and Alzheimer's disease, excitatory amino acid antagonists, neurotropic factors and neuroregenerative agents; tropic factors, drugs aimed at the treatment of CNS trauma or stroke; drugs for the treatment of addiction and drug abuse; antacoids and anti-inflammatory drugs; chemotherapeutic agents for parasitic infections and diseases caused by microbes; immunosuppressive agents and anticancer drugs; hormones and hormone antagonists; heavy metals and heavy metal antagonists; antagonists for non-metallic toxic

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agents, cytostatic agents for the treatment of cancer; diagnostic substances for use in nuclear medicine; immunoactive and immunoreactive agents; transporter inhibitors; antibiotics; antispasmodics; antihistamines; antinauseants; relaxants; stimulants; sense and antisense oligonucleotides; cerebral dilators; psychotropics; antimaniacs; vascular dilators and constrictors; athypertensives; drugs for migraine treatment; hypnotics; hyperglycemic and hypoglycemic agents; minerals and nutritional agents; anti-obesity drugs; anti-asthmatics; and mixtures thereof.

116. (currently amended) The method of claim 115, wherein ~~said~~ the psychiatric disorders comprise depression and schizophrenia.

117. (currently amended) The method of claim 102, wherein ~~said one or more~~ the physiologically effective substances are selected from the group consisting of drugs acting at synaptic sites and neuroeffector junctional sites, general and local analgesics; hypnotics and sedatives, drugs for the treatment of psychiatric disorder; anti-epileptics and anti-convulsants; drugs for the treatment of Parkinson's and Huntington's disease, aging and Alzheimer's disease, excitatory amino acid antagonists, neurotropic factors and neuroregenerative agents; tropic factors, drugs aimed at the treatment of CNS trauma or stroke; drugs for the treatment of addiction and drug abuse; antacoids and anti-inflammatory drugs; chemotherapeutic agents for parasitic infections and diseases caused by microbes; immunosuppressive agents and anticancer drugs; hormones and hormone antagonists; heavy metals and heavy metal antagonists; antagonists for non-metallic toxic agents, cytostatic agents for the treatment of cancer; diagnostic substances for use in nuclear medicine; immunoactive and immunoreactive agents; transporter inhibitors; antibiotics; antispasmodics;

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antihistamines; antinauseants; relaxants; stimulants; sense and antisense oligonucleotides; cerebral dilators; psychotropics; antimaniacs; vascular dilators and constrictors; atihypertensives; drugs for migraine treatment; hypnotics; hyperglycemic and hypoglycemic agents; minerals and nutritional agents; anti-obesity drugs; anti-asthmatics; and mixtures thereof.

118. (currently amended) The method of claim 117, wherein ~~said~~ the psychiatric disorders comprise depression and schizophrenia.

119. (currently amended) The method of claim 101, wherein ~~said~~ the diagnostic substance is selected from the group consisting of substances for nuclear medicine and radiation therapy.

120. (currently amended) The method of claim 102, wherein ~~said~~ the diagnostic substance is selected from the group consisting of substances for nuclear medicine and substances for radiation therapy.

121. (currently amended) The method of claim 101, wherein ~~said~~ the medium ~~allowing~~ allows the transport of ~~said~~ the nanoparticles to the target within ~~said mammal~~ the patient after administration is selected from the group consisting of water, physiologically acceptable aqueous solutions containing salts or buffers or a mixture thereof, and any other solution acceptable for administration to ~~a mammal~~ the patient.

122. (currently amended) The method of claim 102, wherein ~~said~~ the medium ~~allowing~~ allows the transport of ~~said~~ the nanoparticles to the target within ~~said the~~ mammal after administration is selected from the group consisting of water, physiologically

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acceptable aqueous solutions containing salts or buffers or a mixture thereof, and any other solution acceptable for administration to ~~a mammal~~ the patient.

Claims 123-131 (canceled)

132. (currently amended) The method of claim 101, wherein ~~said~~ the nanoparticles are made of polybutylcyanoacrylate.

133. (currently amended) The method of claim 102, wherein ~~said~~ the nanoparticles are made of polybutylcyanoacrylate.

Claim 134 (canceled)

135. (new) The method of claim 102, wherein the polymerization step is selected from the group consisting of emulsion polymerization, interfacial polymerization, solvent deposition, solvent evaporation, and crosslinking oligomers or polymers or both, in solution.

136. (new) The method according to claim 102, wherein, in the polymerization step, a polymeric material is formed which is selected from the group consisting of polyacrylates, polymethacrylates, polyarylamides, polyacetates, polyglycolates, polyanhydrides, polyorthoesters, gelatin, polysaccharides, albumin, polystyrenes, polyvinyls, polyacrolein, polyglutaraldehydes and copolymers and mixtures thereof.